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Outcomes of Stage III NSCLC with occult primary vs. known primary lesions

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ABSTRACT

Objectives: Occult primary non-small cell lung cancer (OP-NSCLC) involving mediastinal lymph nodes without an identifiable primary tumor is a rare presentation, with little known about how outcomes compare to typical Stage III NSCLC. We reviewed our experience treating OP-NSCLC with definitive radiotherapy and compared outcomes to a contemporary cohort of stage III NSCLC patients.

Materials and methods: We reviewed 605 patients with stage III NSCLC staged with PET-CT and treated with definitive radiotherapy between 1998 and 2013. Overall survival, intrathoracic control, and freedom from distant metastasis were computed using Kaplan-Meier method and logrank comparison. Cox hazard ratios were used to perform univariate and multivariate analyses.

Results: Twenty-one patients were identified with OP-NSCLC (3.5%). Patients with OP-NSCLC, as compared to known primary NSCLC, had significantly better 5-year rates of intrathoracic control (83.5% vs. 24.2%, $P < 0.001$), freedom from distant metastasis (59.0% vs. 26.3%, $P = 0.003$), and overall survival (61.6% vs. 15.2%, $P < 0.001$). Multivariate analyses confirmed occult primary as an independent prognostic factor associated with a 70% reduction in risk of intrathoracic failure, a 55% reduction in risk of distant metastasis, and a 70% reduction in risk of death.

Conclusion: To our knowledge, this is the largest reported series of OP-NSCLC and the first to compare it to a contemporary cohort of Stage III NSCLC with known primary lesion. Definitive radiation therapy was associated with favorable locoregional control and survival, particularly compared with typical stage III NSCLC. This difference suggests that occult primary NSCLC may be a distinct entity with different biology than typical NSCLC.

1. Introduction

Non-small cell lung cancer (NSCLC) involving mediastinal lymph nodes without an identifiable primary tumor (*i.e.* occult primary NSCLC or OP-NSCLC) is an uncommon presentation and rare diagnosis. To date there are fewer than 100 cases reported in the literature, most of which are single patient case reports [1–7]. OP-NSCLC is defined as the absence of an identifiable primary lung tumor, in the setting of mediastinal lymph node pathology consistent with a tumor arising from the lung. Therefore, a detailed and thorough staging workup is necessary to rule out metastatic involvement from a non-thoracic primary site. Occult primary NSCLC is sometimes referred to in the literature as mediastinal lymph node carcinoma of unknown primary site, though it is important to distinguish between occult primary NSCLC and those in which the cell of origin is truly unknown (*i.e.* could represent a non-lung primary as well).

Given their rarity and the fact that appropriate treatment strategies are not well established, OP-NSCLC is often treated in the same manner as NSCLC with an identifiable primary tumor, namely with definitive surgery or radiotherapy and sequential or concurrent chemotherapy. However, the prognosis for OP-NSCLC patients and patterns of failure remain poorly defined. The purpose of this study was to review our institutional experience in OP-NSCLC patients and compare outcomes to stage III NSCLC patients with an identifiable primary treated with definitive radiation therapy.

2. Materials and methods

The institutional review and privacy boards approved this retrospective study with a waiver of informed consent. Patient

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confidentiality was maintained as required by the Health Insurance Portability and Accountability Act. Between 1998 and 2013, 1103 patients were treated with definitive radiotherapy for stage III NSCLC. Patients treated to less than 45 Gy (n = 48) were excluded as this represented treatment with palliative rather than curative intent. We also excluded those who did not have an evaluable pre-treatment PET-CT (n = 450), to ensure that results would be representative of contemporary practice in which all patients, particularly those with occult primary tumors, would undergo PET-CT staging. All patients were treated with conventionally fractionated radiation therapy, with or without chemotherapy.

OP-NSCLC was defined as a pathologically definitive diagnosis of NSCLC based on mediastinal nodal biopsy, with no identifiable lung primary on PET-CT and diagnostic chest CT, and no diagnosis of other cancer within the preceding 5 years. All patients had centralized pathology review by a thoracic pathology specialist confirming a diagnosis of non-small cell lung cancer. Patients were staged according to the AJCC 7th edition.

Comparisons between cohorts were performed using either the chi-square test or a 2-tailed Student's *t*-test. Intrathoracic and distant failure was defined as tumor recurrence in the lung parenchyma, mediastinal lymph nodes, and/or pleura or development of secondary sites of disease outside the thoracic cavity, respectively. Death was defined as death due to any cause including cancer and non-cancer events. The Kaplan Meier method, with logrank comparison was used to calculate overall survival (OS), intrathoracic control (ITC), and freedom from distant metastasis (FDM) from the end of radiotherapy. Cox hazard ratios were performed to conduct univariate analysis (UVA) and multivariate analyses. Any category with a *P* value less than 0.100 on univariate analysis was included in the multivariate model. A probability of less than 0.050 was considered statistically significant. Analyses were performed in SPSS statistics version 21 (IBM, Armonk, NY, USA) and/or Prism version 7 (GraphPad Software Inc, La Jolla, CA, USA).

3. Results

3.1. Patient, tumor, and treatment characteristics

605 evaluable patients were included in the analysis. The median age was 66 years and the median follow-up for patients alive at time of analysis was 43 months. Twenty-one cases with occult primary were identified (3.5%). To confirm the classification of OP-NSCLC, a thoracic pathologist performed another review of available cases (n = 13), revealing that in nine cases a lymphocytic background was present, consistent with a lymph node metastasis from an unknown primary. The remaining cases were considered to be lymph nodes entirely replaced by tumor based on radiologic findings.

There was no significant difference between the occult primary and known primary group with respect to age, gender, performance status, or smoking history, Table 1. In the OP-NSCLC group, 9 patients (43%) had adenocarcinoma, 9 (43%) had squamous cell carcinoma, and 3 (14%) had NSCLC not otherwise specified. The median number of nodal stations involved in OP-NSCLC patients was 3 (range, 1–7) and the median number of involved nodes was 4 (range 2–10). The median size of the largest involved node was 3.0 cm (range 1.2–5.6 cm). Invasive mediastinal staging (mediastinoscopy or endobronchial ultrasound) was performed in 62% (n = 13) of OP-NSCLC patients; the remaining patients were assigned nodal stage based on PET-CT results. All but one patient received chemotherapy, 13 (62%) in a sequential fashion and 7 (33%) in a concurrent fashion. In general, patients treated with chemotherapy received a platinum doublet regimen. The median radiation dose for OP-NSCLC patients was 62.0 Gy.

Table 1
Tumor characteristics.

Characteristic	All patients *Number (%)*	Occult Primary	Known Primary
AJCC Tumor Disease Category			
T0	21 (3.5%)	21 (100.0%)	0 (0.0%)
T1	126 (20.8%)	0 (0.0%)	126 (21.6%)
T2	169 (27.9%)	0 (0.0%)	169 (28.9%)
T3	148 (24.5%)	0 (0.0%)	148 (25.3%)
T4	141 (23.3%)	0 (0.0%)	141 (24.1%)
AJCC Nodal Disease Category			
N0	32 (5.3%)	0 (0.0%)	32 (5.5%)
N1	23 (3.8%)	0 (0.0%)	23 (3.9%)
N2	314 (51.9%)	9 (42.9%)	305 (52.2%)
N3	236 (39.0%)	12 (57.1%)	224 (38.4%)
AJCC Stage			
IIIA	303 (50.1%)	9 (42.9%)	294 (50.3%)
IIIB	302 (49.9%)	12 (57.1%)	290 (49.7%)
Histology			
Adenocarcinoma	340 (56.2%)	9 (42.9%)	331 (56.7%)
Squamous cell carcinoma	194 (32.1%)	9 (42.9%)	185 (31.7%)
NSCLC not otherwise specified	64 (10.6%)	3 (14.3%)	61 (10.4%)
Large cell lung carcinoma	7 (1.2%)	0 (0.0%)	7 (1.2%)
EGFR classification			
Altered	19 (3.1%)	0 (0.0%)	19 (3.3%)
Unaltered	231 (38.2%)	10 (47.6%)	221 (37.8%)
Not tested	355 (58.7%)	11 (52.4%)	344 (58.9%)

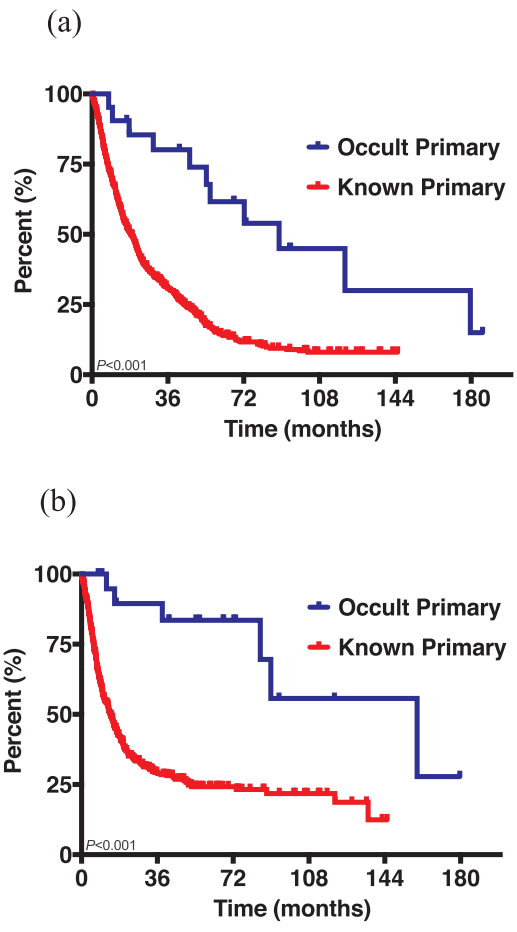

Fig. 1. (a) Overall survival. (b) Intrathoracic control.

3.2. Overall survival (OS)

The 5-year actuarial OS was 16.9%. Patients with OP-NSCLC had a significantly better 5-year OS as compared to those with known primary NSCLC (61.6% vs. 15.2%, $P < 0.001$), Fig. 1**a.** On univariate analysis, occult primary was associated with significantly improved OS (HR for death = 0.288, $P < 0.001$). Other factors significantly associated with improved survival on univariate analysis were performance status (KPS ≥ 80), use of chemotherapy, RT dose (≥ 60Gy), and tobacco use (never-smoker). Younger age was nonsignificantly associated with improved survival ($P = 0.09$). These factors were incorporated into a multivariate analysis. This showed that occult primary status remained significantly associated with improved survival (HR for death = 0.312, $P < 0.001$). Better performance status, higher RT dose, and never-smoker status remained significant on multivariate analysis while age and chemotherapy use did not.

3.3. Intrathoracic control (ITC)

The overall 5-year ITC rate was 27.0%; OP-NSCLC patients had a significantly improved 5-year ITC rate (83.5% vs. 24.2%, $P < 0.001$), Fig. 1**b.** On univariate analysis, occult primary, RT dose, and tobacco use were significantly associated with ITC. On multivariate analysis, occult primary remained significantly associated with ITC, with a hazard ratio of 0.274 ($P = 0.002$).

The median time to intrathoracic progression was 159.4 months in OP-NSCLC patients as compared to 13.8 months in known primary NSCLC patients. Of the 6 OP-NSCLC patients who failed intrathoracically, 4 recurred in the mediastinal lymph nodes alone, 1 had new disease simultaneously in the lung and pleura and 1 patient had new disease in the pleura. There were no isolated primary parenchymal lung recurrences.

3.4. Freedom from distant metastases (FDM)

The 5-year FDM was 26.2%; OP-NSCLC patients had a significantly improved 5-year FDM compared to known primary NSCLC patients (59.0% vs. 26.3%, $P = 0.003$), respectively. On univariate analysis, occult primary, Stage IIIA vs. IIIB, and RT dose were significantly associated with FDM. On multivariate analysis, occult primary remained significantly associated with FDM, with a hazard ratio of 0.437 ($P = 0.015$).

The median time to development of distant metastases was 84.9 months versus 13.0 months in OP-NSCLC versus known primary NSCLC. The site of failure in the 9 OP-NSCLC patients who developed distant metastases were the adrenal gland (n = 3), brain (n = 2), bone (n = 2), mesenteric lymph nodes (n = 1), and bilateral pleural effusions (n = 1).

4. Discussion

OP-NSCLC is a rare entity with fewer than 100 cases reported in the literature. In our institutional experience, OP-NSCLC comprised only 3.5% of all PET-CT staged patients receiving definitive radiation for stage III disease. Occult primary was an independent prognostic factor resulting in a 70% reduction in intrathoracic failure, 55% reduction in distant metastases, and a 70% reduction in death. These data were surprising, as generally patients with cancer of unknown primary site have been reported to have worse survival and treatment outcomes as compared to carcinomas of known primary site [4,8,9].

It is interesting that the pattern of intrathoracic failure was largely restricted to mediastinal lymph node recurrences with no isolated intraparenchymal lung recurrences. This was particularly surprising as elective lung and nodal irradiation was not utilized. In fact the median time to intrathoracic failure was 160 months and therefore these rare events more likely represent a new primary tumor rather than tumor recurrence.

There are multiple hypotheses regarding the origin of OP-NSCLC [1,4,5]. One hypothesis is that the primary tumor is too small to be identified. Historically this may have been a compelling hypothesis, but current staging methodologies have rapidly advanced the ability to detect sub-centimeter tumors that previously would have gone unidentified. The dearth of subsequent lung parenchymal failures in our cohort, even with very long followup, argues against this hypothesis. Another possibility is that these tumors arise from transformed ectopic benign epithelial inclusions within lymph nodes. Alternatively, this entity might simply be attributable to spontaneous primary tumor regression. This speculative theory suggests a role for immunosurveillance in cancer development, particularly in light of recent studies demonstrating NSCLC response to immunotherapy and RT-induced abscopal effects reported in several types of cancer, including NSCLC [10].

Whatever the underlying reasons for this unique presentation, it appears evident that the prognosis and natural history of OP-NSCLC differs significantly from that of known primary NSCLC. The markedly favorable outcomes we observed strongly support the use of a curative treatment approach involving radiotherapy in these patients. Their unusually long survival and relatively low rates of both intrathoracic and distant relapse make this entity clinically distinct not only from typical Stage III NSCLC, but from other carcinomas with unknown primary lesions, and suggest a unique underlying biology that requires further study to elucidate.

Conflict of interest statement

PBR has received honorarium from Corning, served as a consultant for AstraZeneca, and is a consultant for EMD Serono. AJW has received honoraria from AlphaTau Medical, served as a consultant for AstraZeneca, and research grants from CivaTech Oncology.

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